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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/732	12/08/2000	Martin Adamczewski	Mo-6000/LeA 34,147	2900

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EXAMINER	
SCHNIZER, RICHARD A	

ART UNIT	PAPER NUMBER
1635	15

DATE MAILED: 05/07/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/732,680	Adamczewski
Examiner	**Art Unit**
Richard Schnizer	1635

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Feb 13, 2003* .

2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *42 and 43* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *42 and 43* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☒ The drawing(s) filed on *Dec 8, 2000* is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☒ All b) ☐ Some* c) ☐ None of:

1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *8, 14*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

An amendment and a supplemental IDS were received and entered as Paper Nos. 13 and 14, respectively, on 2/13/03.

Claim 45 was canceled as requested.

Claims 42 and 43 remain pending and are under consideration in this Office Action.

Compliance with Sequence Rules

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the following reason(s) set forth in the attached Raw Sequence Listing Error Report.

Rejections Withdrawn

The rejection of claims 42 and 43 under 35 USC 112, second paragraph for lack of antecedent basis are withdrawn in view of Applicant's amendment deleting the passage in question.

After further consideration, the Office Acknowledges that one of skill in the art is enabled to determine percent identity using a variety of algorithms, and would understand that a given percent identity is actually a broad term that can encompass various degrees of identities depending on the parameters of the algorithm. Accordingly the indefiniteness rejection over

percent identity is withdrawn, as the portion of the enablement rejection dealing with the ability of one of skill in the art to calculate percent identity when not supplied with a set of parameters for the GAP program.

Objections Withdrawn

The objection to claim 42 as being drawn to non-elected subject matter is withdrawn in view of Applicant's amendment.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because: the current oath fails to identify the appication by application number.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description

Claims 42, 43, ~~and 45~~ are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, for the reasons of record in Paper No. 25.

Claim is 42 drawn to methods of screening compounds which alter the conductive property of an acetylcholine receptor. Claim 43 is drawn to a method of identifying compounds that bind to an acetylcholine receptor. The methods employ nucleic acids from the following group:

-nucleic acids comprising SEQ ID NO:1;

-sequences which encode any of the amino acid sequences encoded by SEQ ID NO:1

-sequences that encode a polypeptide that is at least 40% identical to SEQ ID NO:2.

The first of these groups of nucleic acids is drawn to a species, nucleic acids comprising SEQ ID NO:1, which is adequately described. Similarly the polypeptide of SEQ ID NO:2 is adequately described. The remaining group is a genus of sequences that encode a polypeptide that is at least 40% identical to SEQ ID NO:2 lacks adequate written description. In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species has been described by complete structure, such as nucleotide sequence, next it is determined whether a representative number of species has been described by other relevant identifying characteristic.

In order to function as intended in the method, all of the nucleic acid sequences must encode an acetylcholine receptor beta subunit which can be assembled into a functional acetylcholine receptor with conductivity properties. The specification describes by complete structure no amino acid sequence, other than SEQ ID NO:2, that fulfills this functional requirement. Neither is any relevant identifying characteristic described, such as a correlation between a specific structure and the required function. The courts have found that merely describing the functional characteristics of a protein encoded by a particular nucleic acid is insufficient to adequately describe the genus of nucleic acids encoding that protein. A gene is a chemical compound, albeit a complex one, and it is well established in our law that conception of a chemical compound requires that the inventor be able to define it so as to distinguish it from other materials, and to describe how to obtain it. See Oka, 849 F.2d at 583, 7 USPQ2d at 1171. Conception does not occur unless one has a mental picture of the structure of the chemical, or is able to define it by its method of preparation, its physical or chemical properties, or whatever characteristics sufficiently distinguish it. In this case, hybridization characteristics and percent homology give no insight as to the functional characteristics of the encoded polypeptides. It is not sufficient to define a nucleic acid or polypeptide solely by its principal biological property, e.g., an acetylcholine receptor beta subunit which can be assembled into a functional acetylcholine receptor, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property. When an inventor is unable to envision the detailed constitution of a gene so as to distinguish it from other materials, conception

has not been achieved until reduction to practice has occurred, i.e., until after the gene has been isolated. Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016, 1021 (Fed. Cir. 1991). The instant application does not provide a written description that would allow one of skill in the art to immediately envisage the specific structure for an acetylcholine receptor beta subunit which can be assembled into a functional acetylcholine receptor. *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed* (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (See *Vas-Cath* at page 1116). Because, there is disclosure of only a single member of the claimed genuses, the skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides and polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The nucleic acid itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

Enablement

Claims 42 and 43 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of screening compounds that alter the conductive property of an acetylcholine receptor comprising SEQ ID NO:2 or fragments of SEQ ID NO:2 that can be assembled into a functional acetylcholine receptor, and for methods of screening compounds that bind to an acetylcholine receptor comprising SEQ ID NO:2 or fragments of SEQ ID NO:2 that can be assembled into a functional acetylcholine receptor, does not reasonably provide enablement for a such methods that employ variants of SEQ ID NO:2 or variants of its fragments. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

As discussed above under Written Description, in order to function in the claimed invention, the recited polynucleotides must encode polypeptides that can be assembled into a functional acetylcholine receptor with conductivity properties. The specification discloses an assay which can be used to measure conductivity, but discloses only a single polypeptide that functions in the claimed invention. It is considered to be routine in the art to perform terminal deletions of nucleic acids in order to determine what is the minimal functional encoded polypeptide. Acetylcholine receptor subunits generally have four transmembrane domains and a ligand binding site (Bossy et al EMBO J. 7(3): 611-618, see e.g. Fig. 3). At a minimum, the role of the beta subunit in conductivity is to form a ligand binding site and a part of a membrane channel that is responsive to ligand binding. It is unrealistic to assume that polypeptides encoding

less than four transmembrane domains and a ligand binding site could encode a polypeptide that could fulfill the minimum function of an acetylcholine receptor subunit. One of ordinary skill in the art appreciates that it takes about 18-20 amino acids to form a single transmembrane domain. Clearly nucleic acids segments as short as 14 bases cannot encode a polypeptide with this function, and would be inoperable in the invention.

The specification fails to provide an enabling disclosure because it fails to teach which variants of SEQ ID NO:2 or its fragments will provide a functional subunits, and which will not. The claims embrace nucleic acids encoding polypeptides that are only 40% identical to SEQ ID NO:2. Guidance in the specification as to which variants will provide a functional beta subunit is limited to a discussion of which amino acid substitutions constitute conservative substitutions. See pages 8 and 9. While it is known that many amino acid substitutions are generally possible in any given protein, certain positions in a polypeptide sequence are critical to the protein's structure/function relationship, such as various sites or regions where the biological activity resides or regions directly involved in binding, stability or catalysis, or which provide the correct three-dimensional spatial orientation for biologically active binding sites, or which represent other properties or characteristics or properties of the protein. These or other regions may also be critical determinants of activity. The prior art teaches that the effects of amino acid substitutions and deletions on protein function were highly unpredictable. Rudinger (In Peptide Hormones J.A. Parsons, Ed. University Park Press, Baltimore, 1976, page 6) teaches that "[t]he significance of particular amino acids and sequences for different aspects of biological activity cannot be

predicted *a priori* but must be determined from case to case by painstaking experimental study." Furthermore Ngo et al (In The Protein Folding Problem and Tertiary Structure Prediction, K. Merz Jr. and S. Legrand, Eds. Birkhauser, Boston, 1994, see page 492) teaches that "[i]t is not known if there exists an efficient algorithm for predicting the structure of a given protein from its amino acid sequence alone. Decades of research have failed to produce such an algorithm". Applicant has provided little or no guidance to enable one of skill in the art to determine, without undue experimentation, the positions in the claimed nucleic acids which are tolerant to change, and the nature and extent to of changes that can be made in these positions in order to retain function as required by the claims. Even if critical residues were identified in the specification, which they are not, the mere identification of these residues as critical would not be sufficient, as the skilled artisan would immediately recognize that critical sites must assume the proper three-dimensional configuration to be active, and that conformation is dependent on surrounding residues as well. Thus alterations in sequences which are not apparently part of a binding site can destroy activity by altering the overall conformation of a protein. One might argue that it would not be undue experimentation to express and assay polypeptides individually using the assays taught in the specification, and thereby empirically determine the function of each one. However as set forth in *In Re Fisher*, 166 USPQ 18(CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and **their performance**

> **characteristics predicted by resort to known scientific laws**; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with the degree of unpredictability of the factors involved.

Emphasis added. The specification fails to provide any theoretical framework which can be used to accurately predict which amino acid substitutions will eliminate receptor function, and which will be tolerated as required by the claims, and no such guidance is available in the art of record. In the absence of such guidance or examples, and in view of the unpredictability of the subject matter and the breadth of the claims, one of skill in the art would have to perform undue experimentation in order to make the invention commensurate in scope with the claims.

Response to Arguments

Applicant's arguments filed 2/13/03 have been fully considered but they are not persuasive.

Applicants requested that the Examiner clarify the outstanding written description rejection with respect to it's reference to "the reasons of record in Paper No. 25". This reference was a typographical error. The previous action was a first action on the merits, and there were at that time no reasons of record for any rejection.

Applicant responded at page 6, paragraph 3 to the written description rejection by indicating that they believed that the amendments to claims 42 and 43 overcome the rejection. This argument is unpersuasive because no reasons were given as to why the amendments

overcame the rejection and the response fails to directly address any of the stated grounds of rejection. The rejections is maintained for the reasons stated above.

Applicant responded to the enablement rejection at pages 8 and 9 of the response. Essentially, Applicant argues that proteins that have greater than 25% structural identity over an alignment of at least 80 amino acids can be presumed to have a similar structure, and the claims are directed to proteins that have at least 40% identity to SEQ ID NO:2 over its entire length. Applicant relies for support on Mittl. This argument is unpersuasive because while it addresses issues of protein folding and general 3-dimensional structure, it fails to address the issue of the effects of point mutations on protein function. The Office has established that certain positions in a polypeptide sequence are critical to the protein's structure/function relationship, such as various sites or regions where the biological activity resides or regions directly involved in binding, stability or catalysis, or which provide the correct three-dimensional spatial orientation for biologically active binding sites, or which represent other properties or characteristics or properties of the protein. While proteins with 40% amino acid identity may have general backbone folding that is similar, the specification fails to teach which of these polypeptides will have the function required to perform the claimed method, i.e. which polypeptide will function as an acetylcholine receptor. For example, SEQ ID NO:2 is a homooligomeric acetylcholine receptor which associates with other identical subunits to form a functional receptor/channel. The specification fails to teach what residues are required for proper recognition of other subunits, which residues are required for ligand binding, and which residues are required for channel

formation. Applicant's arguments fails to address these issues as well, so the rejection is maintained.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 703-306-5441. The examiner can normally be reached Monday through Friday between the hours of 6:20 AM and 3:50 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John Leguyader, can be reached at 703-308-0447. The FAX numbers for art unit 1632 are 703-308-4242, and 703-305-3014. Additionally correspondence can be transmitted to the following RIGHTFAX numbers: 703-872-9306 for correspondence before final rejection, and 703-872-9307 for correspondence after final rejection.

Inquiries of a general nature or relating to the status of the application should be directed to the Patent Analyst Trina Turner whose telephone number is 703-305-3413.

DAVE T. NGUYEN
PRIMARY EXAMINER

Richard Schnizer, Ph.D.